AMENDMENTS TO THE SPECIFICATION

IN THE SPECIFICATION

On page 3, line 21, please replace the original paragraph with the following amended paragraph:

--a) a DNA encoding a protein having the enzymatic activity in hydroxylating the 16-position of the macrolide compound 11107B and selected from the group consisting of a continuous nucleotide sequence from the base 1322 to base 2548 of ~~the sequence No. 1~~ SEQ ID NO: 1; a continuous nucleotide sequence from the base 420 to base 1604 of ~~the sequence number 2~~ SEQ ID NO: 4; and a continuous nucleotide sequence from the base 172 to base 1383 of ~~the sequence number 3~~ SEQ ID NO: 7;--

On page 4, line 25, please replace the original paragraph with the following amended paragraph:

--(d) a DNA encoding ferredoxin and selected from the group consisting of a continuous nucleotide sequence from the base 2564 to base 2761 of ~~the sequence No. 1~~ SEQ ID NO: 1, a continuous nucleotide sequence from the base 1643 to base 1834 of ~~the sequence number 2~~ SEQ ID NO: 4 and a continuous nucleotide sequence from the base 1399 to base 1593 of ~~the sequence number 3~~ SEQ ID NO: 7;--

On page 24, line 19, please replace the original paragraph with the following amended paragraph:

-- (1-1) a DNA selected from those having a continuous nucleotide sequence from the base 1322 to base 2548 of ~~the sequence No. 1~~ SEQ ID NO: 1, a continuous nucleotide sequence from the base 420 to base 1604 of ~~the sequence number 2~~ SEQ ID NO: 4 and a continuous nucleotide sequence from the base 172 to base 1383 of ~~the sequence number 3~~ SEQ ID NO: 7; --

On page 25, line 17, please replace the original paragraph with the following amended paragraph:

-- (2-1) a DNA encoding ferredoxin and selected from the group consisting of a continuous nucleotide sequence from the base 2564 to base 2761 of ~~the sequence No. 1~~ SEQ ID NO: 1, a continuous nucleotide sequence from the base 1643 to base 1834 of ~~the sequence number 2~~ SEQ ID NO: 4 and a continuous nucleotide sequence from the base 1399 to base 1593 of ~~the sequence number 3~~ SEQ ID NO: 7; --

On page 48, line 2, please replace the original paragraph with the following amended paragraph:

--Mix primers 5Dm-3F ~~(sequence No. 4)~~ (SEQ ID NO: 10) and 5Dm-3R ~~(sequence No. 5)~~ (SEQ ID NO: 11) were designed and produced on reference to the amino acid sequence assumed to be that of the cytochrome P450 (CYP105D5) of Streptmyces coelicolor A3 (2). --

On page 50, line 17, please replace the original paragraph with the following amended paragraph:

--On the other hand, primers (6PIN-2F ~~(sequence No. 6)~~ (SEQ ID NO: 12) and 6PIN-2R ~~(sequence No. 7)~~ (SEQ ID NO: 13) were designed and produced based on the nucleotide sequence of the DNA fragment-A1. --

On page 53, line 6, please replace the original paragraph with the following amended paragraph:

--A primer DM-NdeF ~~(sequence No. 8)~~ (SEQ ID NO: 14) obtained by adding a NdeI site to the 5' terminal and a primer DM-SpeR ~~(sequence No. 9)~~ (SEQ ID NO: 15) obtained by adding a SpeI site to the 5' terminal were designed and produced on reference to the nucleotide sequence of ~~the sequence No. 1~~ SEQ ID NO: 1 analyzed in Example 1. Next, these two types of primers (DM-NdeF and DM-SpeR) and the A-1544 strain chromosome DNA obtained in Example 1(1) as a template, were used to run a PCR reaction. The PCR reaction was

accomplished by repeating a two-stage reaction including denaturing carried out at 98°C for 20 seconds and annealing and elongation carried out at 68°C for 2 minutes 30 times by using Takara LA Taq (TAKARA HOLDINGS INC.) and a PCR amplifier (T Gradient, Biometra Co.). --

On page 60, line 22, please replace the original paragraph with the following amended paragraph:

--A primer DM-BglF ~~(sequence No. 10)~~ (SEQ ID NO: 16) obtained by adding a BglII site to the 5' terminal and a primer DM-BglR ~~(sequence No. 11)~~ (SEQ ID NO: 17) obtained by adding a BglII site to the 5' terminal were designed and produced on reference to the nucleotide sequence of ~~the sequence No. 1~~ SEQ ID NO: 1 analyzed in Example 1. --

On page 64, line 15, please replace the original paragraph with the following amended paragraph:

--Mix primers 5Dm-3F ~~(sequence No. 4)~~ (SEQ ID NO: 10) and 5D-1R ~~(sequence No. 12)~~ (SEQ ID NO: 18) were designed and produced on reference to the amino acid sequence estimated as that of the cytochrome P450 (CYP105D5) of Streptmyces coelicolor A3(2). --

On page 66, line 2, please replace the original paragraph with the following amended paragraph:

--The nucleotide sequence of the DNA fragment-A2 obtained in the above (2) was analyzed using a DNA nucleotide sequence analyzer (PE Biosystems 377XL) according to a dye terminator cycle sequence method. As the result of the nucleotide sequence analysis, it was clarified that the DNA fragment-A2 amplified by a PCR reaction had an exact size of 325 bp though it had been found to have a size of about 300 bp by the above measurement using electrophoresis (see the nucleotide sequence 837 to nucleotide sequence 1161 of ~~the sequence number 2~~ SEQ ID NO: 4). Since DNA sequences corresponding to the two types of primers used in the above PCR reaction were found at both ends of the above cloned 325 bp DNA sequence, it was clarified that the DNA fragment-A2 was specifically amplified by these two types of primers (5Dm-3F and 5D-1R) in the above PCR reaction. --

On page 67, line 6, please replace the original paragraph with the following amended paragraph:

--On the other hand, primers (7PIN-2F ~~(sequence No. 13)~~ (SEQ ID NO: 19) and 6PIN-2R ~~(sequence No. 7)~~ (SEQ ID NO: 13) were designed and produced based on the nucleotide sequence of the DNA fragment-A2. --

On page 68, line 9, please replace the original paragraph with the following amended paragraph:

--Each nucleotide sequence of the DNA fragment-B2 and DNA fragment-C2 obtained in the above (4) was analyzed using a DNA nucleotide sequence analyzer (PE Biosystems 377XL) according to a dye terminator cycle sequence method. The nucleotide sequence was thus analyzed to obtain the information of the nucleotide sequence of 2329 bp shown in ~~the sequence number 2~~ SEQ ID NO: 4 from each sequence of the DNA fragment-B2 and DNA fragment-C2. --

On page 68, line 16, please replace the original paragraph with the following amended paragraph:

--An open reading frame (ORF) in this 2329 bp was retrieved, to find that the two kinds of protein were coded. Each amino acid sequence of these proteins was retrieved by the BLAST search, and as a result, an ORF (hereinafter referred to as bpmA) encoding a protein consisting of 395 amino acids having high homology to cytochrome P450 existed in the base 420 to base 1604 of ~~the sequence number 2~~ SEQ ID NO: 4. The bpmA had the highest homology (homology: 67.4%) to the amino acid sequence of the psmA isolated from the A-1544 strain and also had a relatively high homology (homology: 64.8%) to cytochrome P450 soy (Soy C)of Streptmyces griseus. It was considered from this fact that the bpmA highly possibly encoded hydroxyllating enzyme of the cytochrome P-450 type. --

On page 69, line 2, please replace the original paragraph with the following amended paragraph:

--Also, an ORF (hereinafter referred to as bpmB) encoding a protein having a high homology to ferredoxin of a 3Fe-4S type that existed just downstream (the base 1643 to base 1834 of ~~the sequence number 2~~ SEQ ID NO: 4) of the bpmA. The protein encoded by the bpmB consisted of 64 amino acids, and had the highest homology (81.0%) to the amino acid sequence of the psmB isolated from the A-1544 strain and a relatively higher homology (homology: 76.2%) to the amino acid sequence assumed to be that of ferredoxin just downstream of the amino acid sequence assumed to be cytochrome P450 (CYP105D5) of Streptmyces coelicolor A3(2). Therefore, it was considered that the bpmB served to transfer electrons and participated in hydroxylation together with the bpmA. --

On page 69, line 18, please replace the original paragraph with the following amended paragraph:

--A primer 07-NdeF ~~(sequence No. 14)~~ (SEQ ID NO: 20) obtained by adding a NdeI site to the 5' terminal and a primer 07-SpeR ~~(sequence No. 15)~~ (SEQ ID NO: 21) obtained by adding a SPeI site to the 5' terminal were designed and produced on reference to the nucleotide sequence of ~~the sequence number 2~~ SEQ ID NO: 4 analyzed in Example 7. Next, these two types of primers (07-NdeF and 07-SpeR) and the Mcr-11107 strain chromosome DNA obtained in Example 7(1) as a template, were used to run a PCR reaction. The PCR reaction was accomplished by repeating a two-stage reaction including denaturing carried out at 98°C for 20 seconds and annealing and elongation carried out at 68°C for 2 minutes 30 times by using Takara LA Taq (TAKARA HOLDINGS INC.) and a PCR amplifier (T Gradient, Biometra Co.). --

On page 73, line 12, please replace the original paragraph with the following amended paragraph:

--Mix primers (5Dm-3F ~~(sequence No. 4)~~ (SEQ ID NO: 10) and 5Dm-2R ~~(sequence No. 16)~~ (SEQ ID NO: 22) were designed and produced on reference to the amino acid sequence estimated as that of the cytochrome P450 (CYP105D5) of Streptmyces coelicolor A3(2). --

On page 74, line 26, please replace the original paragraph with the following amended paragraph:

--The nucleotide sequence of the DNA fragment-A3 obtained in the above (2) was analyzed using a DNA nucleotide sequence analyzer (PE Biosystems 377XL) according to a dye terminator cycle sequence method. As the result of the nucleotide sequence analysis, it was clarified that the DNA fragment-A3 amplified by a PCR reaction had an exact size of 741 bp though it had been found to have a size of about 750 bp by the above measurement using electrophoresis (see the nucleotide sequence 616 to nucleotide sequence 1356 of ~~the sequence No. 3~~ SEQ ID NO: 7). Since DNA sequences corresponding to the two types of primers used in the above PCR reaction were found at both ends of the above cloned 741 bp DNA sequence, it was clarified that the DNA fragment-A3 was singularly amplified by these two types of primers (5Dm-3F and 5Dm-2R) in the above PCR reaction. --

On page 76, line 6, please replace the original paragraph with the following amended paragraph:

--On the other hand, primers (5PIN-2F ~~(sequence No. 17)~~ (SEQ ID NO: 23) and 6PIN-2R ~~(sequence No. 7)~~ (SEQ ID NO: 13)) were designed and produced based on the nucleotide sequence of the DNA fragment-A3. --

On page 77, line 11, please replace the original paragraph with the following amended paragraph:

--Each nucleotide sequence of the DNA fragment-B3, DNA fragment-C3 and DNA fragment-D3 obtained in the above (4) was analyzed using a DNA nucleotide sequence analyzer (PE Biosystems 377XL) according to a dye terminator cycle sequence method. The nucleotide sequence was thus analyzed to obtain the information of the nucleotide sequence of 1860 bp shown in ~~the sequence number 3~~ SEQ ID NO: 7 from each sequence of the DNA fragment-B3, DNA fragment-C3 and DNA fragment-D3. --

On page 77, line 19, please replace the original paragraph with the following amended paragraph:

--An open reading frame (ORF) in this 1860 bp was retrieved, to find that the two kinds of protein were encoded. Each amino acid sequence of these proteins was retrieved by the BLAST search, and as a result, an ORF (hereinafter referred to as tpmA) encoding a protein consisting of 404 amino acids having high homology to cytochrome P450 existed in the base 172 to base 1383 of ~~the sequence number 3~~ SEQ ID NO: 7. The tpmA had the highest homology (homology: 77.4%) to the amino acid sequence assumed to be that of cytochrome P450 (CYP105D5) of Streptmyces coelicolor A3(2) and also a high homology (homology: 76.6%) to the amino acid sequence of the psmA isolated from the A-1544 strain. It was considered from this fact that the tpmA was highly possibly a gene encoding hydroxylating enzyme of the cytochrome P-450 type. --

On page 78, line 6, please replace the original paragraph with the following amended paragraph:

--Also, an ORF (hereinafter referred to as tpmB) encoding a protein having a high homology to ferredoxin of a 3Fe-4S type existed just downstream (the base 1399 to base 1593 of ~~the sequence number 3~~ SEQ ID NO: 7) of the tpmA. The protein encoded by the tpmB consisted of 65 amino acids, and had the highest homology (81.0%) to the amino acid sequence of the psmB isolated from the A-1544 strain and also a high homology (homology: 82.5%) to the amino acid sequence assumed to be that of ferredoxin just downstream of the amino acid sequence assumed to be cytochrome P450 (CYP105D5) of Streptmyces coelicolor A3 (2). Therefore, it was considered that the tpmB served to transfer electrons and coded ferredoxin participating in hydroxylation together with the tpmA. --

On page 78, line 22, please replace the original paragraph with the following amended paragraph:

--A primer tpm-NdeF ~~(sequence No. 18)~~ (SEQ ID NO: 24) obtained by adding a NdeI site to the 5' terminal and a primer tpm-SpeR ~~(sequence No. 19)~~ (SEQ ID NO: 25) obtained by

adding a SPeI site to the 5' terminal were designed and produced on reference to the nucleotide sequence of the SEQ ID NO: 7 analyzed in Example 10. Next, these two types of primers (tpm-NdeF and tpm-SpeR) and the A-1560 strain chromosome DNA obtained in Example 10(1) as a template, were used to run a PCR reaction. The PCR reaction was accomplished by repeating a two-stage reaction including denaturing carried at 98°C for 20 seconds and annealing and elongation carried out at 68°C for 2 minutes 30 times by using Takara LA Taq (TAKARA HOLDINGS INC.) and a PCR amplifier (T Gradient, Biometra Co.). --

AMENDMENTS TO THE SEQUENCE LISTING

IN THE SEQUENCE LISTING

Please replace the Sequence Listing of record with the Substitute Sequence Listing enclosed herewith.